

# Role of Antibodies: A Novel Paradigm in Mathematical Modeling for Cancer Treatment

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## Abstract

A mathematical model for the quantitative analysis of cancer immune interaction, considering the role of antibodies has been proposed in this paper. The model is based on the clinical evidence, which states that antibodies can directly kill cancerous cells [1]. The existence of transcritical and saddle-node bifurcation, which has been proved using *Sotomayor theorem*, provides strong biological implications. Through numerical simulations, it has been illustrated that under certain therapy (like monoclonal antibody therapy), which is capable of altering the parameters of the system, cancer-free state can be obtained.

*Key words:* Cancerous cells, B-cells, Plasma cells, Antibodies, Transcritical bifurcation, Saddle-node bifurcation

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## 1 Introduction

Cancer is a leading cause of death worldwide. It is predicted to remain so for years to come unfortunately. It is a disease which is caused by the abnormal function of our own cells. Cancer is not a single disease; it comprises more than 200 diseases [2,3] which share common characteristics, that is, they are abnormal cells where the normal processes which regulate normal cell proliferation, differentiation and death (cell apoptosis) are interrupted. The causes of cancer are changes that cause normal cells to acquire abnormal functions. These causes may be the result of inherited mutation or environmental factors such as tobacco products, ultraviolet radiation, X-rays, chemicals, etc [3]. A normal cell can be transformed into a cancerous cell when certain genes are activated or inactivated because of these mutation and environmental factors. In cancerous cells the normal control system that prevent abnormal cell growth and differentiation and the invasion of other tissues and organs are disabled.

The immune system, which is a complex network of cells, cytokines, lymphoid tissues and organs that work together, helps the host in fighting against pathogenic micro organisms and cancerous cells. When cancerous cells proliferate to a detectable threshold number in a given physiological space of the human anatomy, the body's own immune system is triggered into a search and destroy mode [4]. The various components of the immune system interact with each other and the cancerous cells to prevent our body from cancer and they also help in preventing the occurrence, development and recurrence of cancer. But sometimes cancerous cells are able to overcome the limitations imposed by the immune system and are able to successfully proliferate and propagate in the human body. The defense mechanisms of the human body against external invaders and other pathogens has two major components; innate (or natural) and adaptive (or acquired) immune systems. The innate immune system comprises cells and mechanisms that defend the human body from infection by other organisms and pathogens in a non specific manner. Innate immune responses are stimulated by structures that are common to groups of related pathogenic agents and may not distinguish fine differences among foreign substances and it does not confer long lasting or protective immunity in our body.

The major components of innate immune system are natural killer (NK) cells, dendritic and mast cells, macrophages and natural antibody producing cells. This immune system which is naturally present in our body even in the absence of external invaders or cancerous cells, provide immediate defense against infection. The biological mechanisms of innate immune system are integrated with that of adaptive immune system by stimulating and influencing the nature of the adaptive immune responses. The acquired immune responses are highly specific for a particular pathogen. These immune responses are charac-

terized by an exquisite specificity for distinct external invaders and pathogens and the ability to remember and respond more vigorously to repeated exposures to the same pathogens. Adaptive immune system responses against external invaders and pathogens are mediated by a special group of immune cells called lymphocytes through either the anti-body (humoral) mediated or cell-mediated immune responses [2,4]. The most important cells in acquired immune system are lymphocytes, which are small round cells that are found in blood, lymph and connective tissue. The two major components of lymphocytes are the B-cells and the T-cells [5]. Both B-cells and T-cells are derived from the stem cells residing in the bone marrow. Cells which are destined to become T-lymphocyte undergo further differentiation in the thymus while the precursors of B-lymphocyte differentiate in other lymphoid organs. The B-lymphocytes are responsible for antibody mediated immune response and the T-lymphocytes are responsible for cell-mediated immune responses.

The theoretical study of cancer-immune dynamics, which has a long history, has been done by many authors [6,7,8,9,10,11,12,13,14,15,16,17,18]. We first look through some of the existing mathematical models of the cancer-immune system interactions. Kuznetsov and Taylor [6] presented a mathematical model of the cytotoxic T-lymphocyte and responses to the growth of an immunogenic tumor. They studied the immune-stimulation of tumor growth, "sneaking through" of the tumor and the formation of a tumor dormant state. Through mathematical modeling Kirschner and Panetta [9] have illustrated the dynamics between tumor cells, immune effector cells and interleukin-2 (IL-2). Their efforts explain both short-term tumor oscillations in tumor size as well as long-term tumor relapses. Bodnar and U.Fory's [10] studied the periodic dynamics in the mathematical model of the immune system. In Murchuk's model of immune system dynamics, U.Fory's [11] presented the model of a general immune system reaction. The qualitative behavior of the solution to the model (and its application), along with many illustration of the recovery process, oscillations or lethal outcomes of the disease has been discussed. In [14], the authors expressed the spontaneous regression and progression of a malignant tumor system as a prey-predator like system, where the tumor (cancerous cells) is treated as prey and the cytotoxic T-lymphocytes as predator. The deterministic model is extended to a stochastic one, allowing random fluctuations around the positive interior equilibrium. The stochastic stability properties of the model are investigated both analytically and numerically. Mallet and De Pillis [15] have presented a hybrid cellular automata partial differential equation model of moderate complexity to describe the interaction between tumor and the immune systems of the host. Chaplain et. al. [16] have explained the effect of time and space in tumor immunology using mathematical model, that is, the spatio-temporal phenomena. The role of interleukin-2 (IL-2) in tumor dynamics is illustrated through mathematical modeling (a modified version of the Kirshner-Panetta model) in [17], where the author has shown that interleukin-2 alone can cause the tumor cell population to regress.

In [18], the global dynamics of Kirshner-Panetta model is explored and under what conditions tumor clearance can be achieved, is obtained.

In most of these tumor-immune system interaction models, the immune system comprises both antibody mediated and cell mediated immune responses. In such situations, it is difficult to identify which immune system plays greater role in the elimination or control of the cancerous cells. In this paper we have investigated the role of antibodies in the eradication of the cancerous cells using system of non linear differential equations. The motivation came from the fact that researchers at the University of Manchester along with their collaborators at the University of Southampton investigated how antibody treatments make cancerous cells kill themselves and found a previously undiscovered mechanism that could, in future, be even more effective in causing their death. It is known that when antibodies bind to cells, including cancerous cells, they can mark those targets for destruction by the body's immune system but Tim Illidge et. al. [1] have shown in their latest study that antibodies can kill cancerous cells directly. When the antibodies binds with cancerous cells, it causes lysosomes (small acid containing sacs) inside the cell to swell and burst rapidly releasing their toxic contents with fatal results for cancerous cells, which is non-apoptotic in nature.

Not much work has been done on the role of antibodies to eradicate cancerous cells through mathematical modeling. This may be due to the fact that no clinical evidence was available to support the fact that antibodies are actually capable of killing cancerous cells directly. To the best of our knowledge, the role of antibodies to eradicate cancer by mathematically modeling the scenario were done by Dillman and Koziol [19], Kolev [20] and Dubey et. al. [21]. Dillman and Kziol proposed and developed a pharmacokinetic model for the quantitative analysis of dose-time-cell survival curves devolving from infusions of the murine monoclonal antibody T1O1 into patients with chronic lymphocytic leukemia (CLL) and cutaneous T cell lymphoma (CTCL). Kolev has described a model of cellular tumor dynamics in competition with the immune system with the help of integrodifferential equations, where the role of antibodies has been taken into account. Dubey et. al. have considered many components of acquired immune response, namely, T Helper cells, Cytotoxic T-Cells, B-cells which secretes antibodies and their interaction with avascular cancer cells. They observed that under appropriate conditions this interaction is capable of controlling the growth of cancerous cells.

In section 2, the whole biological scenario supported by schematic diagram is explained, followed by mathematical formulation of the model. Estimation of the system parameters are discussed in section 3. Linear stability analysis, global stability analysis as well as bifurcation analysis of the system are explored in section 4. Section 5 deals with the numerical results and their biological implications. The paper ends with a conclusion.

## 2 Model Formulation

The host immune system has the ability to produce some significant anti cancerous immune responses, one of which is the B-cells. The human body produces millions of different B-cells each day that circulates in the blood and lymphatic system performing the role of immune surveillance. The principal function of B-cells is to secrete antibodies against antigens. Prior to stimulation by either antigen or mitogen, B-cells are morphologically small cells. The binding of antigen to antigen receptors (i.e. antibodies) on B-cells can result in the activation and differentiation of small B-cells into large B-cells which secrete antibodies at a lower rate. A set of immunoglobulin molecules is present on the surface of unstimulated B-cells [22]. By binding to these immunoglobulin receptors and with a possible second signal from an accessory cell such as the T-cell, the antigen stimulates the B-cell to divide and mature into terminal (non-dividing) antibody secreting cells called plasma cells. The plasma cells are most active in secreting antibodies at a much faster rate but large B-lymphocytes, which proliferate rapidly, also secrete antibody, albeit at a lower rate. Some of the large B-cells eventually revert back to small B-cells where they probably function as memory cells, which can respond vigorously to subsequent antigenic challenges [5]. The secreted antibodies then circulate in the blood and lymphatic system, and bind to the original antigen, marking them for elimination by several mechanisms, including activation of the complement system, promotion of phagocytosis via opsonization and mediation of antibody dependent cell-mediated cytotoxicity (ADCC) with effector cells such as macrophage, NK cells and neutrophils.

Based on the above biological scenario and from the clinical evidence that antibodies can directly kill cancerous cells [1], we present a schematic diagram (fig.1) to describe the interaction between the cancerous cells, large B-cells, plasma cells and antibodies. We now propose a mathematical model to describe the interaction between the host immune system considering the role of humoral mediated immune responses, that is, the antibodies, and the cancerous cells.

Let  $L$ ,  $P$ ,  $A$  and  $T$  be the number of large B-cells, plasma cells, antibodies and the cancerous cells respectively at any time  $t_1$ . It has been observed that the number of antibody forming cells per spleen increased from the order of  $10^2$  to  $10^6$  over 96 hours when a single injection of sheep red blood cells is given to mice [23]. However, when the absolute number of responding cells reaches the order of  $10^7$ , density dependent effects may prevent further growth of the lymphocyte population [24,25]. Therefore, we assume that the large B-cells grow logistically. The large B-cells can either proliferate with constant intrinsic growth rate  $a_1$  and increase the B-cell population or they can undergo further differentiation into plasma cells at a constant rate  $b_1$ . We assume  $a_1 > b_1$  to

insure that there can be a net growth in the large B-cells population. Thus, the governing equation for the large B-cells and the plasma cells are given by

$$\frac{dL}{dt_1} = a_1 u L \left(1 - \frac{L}{K_1}\right) - b_1(1 - u)L, \quad (1)$$

$$\frac{dP}{dt_1} = b_1(1 - u)L - \mu_1 P, \quad (2)$$

where,  $u$  ( $0 < u < 1$ ) is the fraction of the large B-cells which remains as the proliferating large B-cells and  $(1 - u)$  is the fraction that differentiate into plasma cells,  $K_1$  is the carrying capacity of the large B-cell population and  $\mu_1$  is the natural death rate of the plasma cells.

It is clinically known that both the large B-cells as well as the plasma cells secrete antibodies, however, plasma cells secrete them at a much faster rate than the large B-cells. Therefore, the governing equation for the the antibody is given by

$$\frac{dA}{dt_1} = r_1 L + r_2 P - \mu_2 A - \beta_1 AT, \quad (r_1 < r_2), \quad (3)$$

where  $r_1$  and  $r_2$  are the rate at which the large B-cells and the plasma cells secrete antibodies respectively,  $\mu_2$  is the natural death rate of antibodies and  $\beta_1$  the rate at which the cancerous cells kill the antibodies.

We assume that the cancerous cells grow logistically in the absence of the antibodies and the antibodies kill the cancerous cells directly [1]. Thus for the cancerous cells, the governing equation is

$$\frac{dT}{dt_1} = rT \left(1 - \frac{T}{K_2}\right) - \beta_2 AT, \quad (4)$$

where  $r$  is the intrinsic growth rate,  $K_2$  is the carrying capacity of the cancerous cells and  $\beta_2$  is the rate at which the antibodies kill the cancerous cells by direct interaction. The initial conditions for systems (1 – 4) are  $L(0) = L_0$ ,  $P(0) = P_0$ ,  $A(0) = A_0$  and  $T(0) = T_0$  respectively.

### 3 Parameter Estimation

Appropriate parameter values determine the analysis and behavior of a mathematical model to describe a given system. Therefore, to complete the development of our mathematical model, we estimate the values of the system

parameters in the following manner. The mean generation time for large B lymphocyte is approximated to be 6 to 48 hours [26]. Hence the growth rate  $a_1$  of the large B lymphocyte is estimated to be between 0.02 and  $0.2 \text{ hr}^{-1}$  [5]. Since the immune response to a T-independent antigen generally lacks any detectable immunological memory [27,28], the conversion of large lymphocytes back into small lymphocytes and the possible subsequent recycling of memory cells back into large lymphocytes have not been explicitly considered. The life time of plasma cells ranges from few days to few weeks. Thus the natural death rate  $\mu_2$  of the plasma cells is approximated to vary between 0.002 to  $0.02 \text{ hr}^{-1}$  [5].

The plasma and large B cells secrete antibodies at different rates. It is known that the plasma cells may be even 100 fold more active in immunoglobulin synthesis than the large B cells [29]. Thus, the rate at which the plasma cells secrete antibodies can be estimated to be 2 to 100 times that of the large B cells. The secretion rate of antibodies by a single cell also varies considerably. Different authors estimated the absolute rate of antibody secretion by a single cell. For example, Nossal and Makela [30] have been found in vitro that the rate at which a single cell secretes antibodies ranges from 100 to 1500 antibodies  $\text{cell}^{-1}\text{sec}^{-1}$ . Conrad and Ingraham [31] found in vivo values that range from 8000 to 20000 antibodies  $\text{cell}^{-1}\text{sec}^{-1}$ .

The dynamics of cancerous cell (tumors) growth has been studied by numerous authors (V.A. Kuznetsov et. al [6], L.G. Pillis and A. Randunskaya [32], D. Krischner and J. C. Panetta [9], S. Banerjee and R.R. Sarkar [17]. They described the dynamics of tumor cell growth using the logistic growth function as  $dT/dt = rT(1 - T/K_2)$  in the absence of the immune responses, where  $r$  is the intrinsic growth rate and  $K_2$  is the carrying capacity. L. G. Pillis et. al. [33] estimated the parameter values for  $r$  and  $K_2$  by using the least-squares distance method and using optimization software with the data in Diefenbach et. al. [34]. In our case, we use  $r = 0.431 \text{ days}^{-1}$  and  $K_2 = 9.8 \times 10^8$  cells from [33] for the analysis of our model. The interaction terms between antibodies and cancerous cells, namely,  $\beta_1$  and  $\beta_2$  and the natural death rate of antibodies, that is,  $\mu_2$  are estimated using synthetic data.

To generate synthetic data, we consider the research article by L.G. de. Pillis et al. [33]. We first generate a figure (see fig. 2a) taking human data, patient 9, as given in table 2 of [33]. This figure (see fig.2a) reflects the behavior of the model by De Pillis et. al. [33], who have used parameters taken from experimental results of patient from Rosenberg's study on metastatic melanoma. In the generated figure, they have investigated a  $10^6$  cells tumor, a tumor level that in silico innate immune system cannot control on its own. The figure shows the effect of immunotherapy alone against the tumor, namely, a TIL (tumor infiltrating lymphocyte) injection, followed by short doses of IL-2. Using DataThief ([www.datathief.org](http://www.datathief.org)), the data for cancerous cells decay

are extracted (say, for 20 time points) and some noise is added to the data, which we name as observed values,  $T_{obs}$  (say). To start the estimation process, we initially choose (within meaningful biological range) the values of the parameters to be estimated, namely,  $\beta_1, \beta_2$  and  $\mu_2$  arbitrarily. Next, we solve the equations (1 – 4) numerically with these initial values of the parameters and obtain the solution of the model at those time points, where the observed values have been obtained, which we name as calculated values,  $T_{cal}$  (say). We now use least square method to minimize the sum of the residuals, namely,  $\sum_{i=1}^{20} (T_{cal}^{(i)} - T_{obs}^{(i)})^2$  to obtain the estimated values of the system parameters, namely,  $\beta_1, \beta_2$  and  $\mu_2$ . In practise, a MATLAB code has been developed to carry out the above process and the estimated values of the parameters are obtained as  $\beta_1 = 2.5448 \times 10^{-6}$ ,  $\beta_2 = 2.4935 \times 10^{-7}$  and  $\mu_2 = 0.1277$ . Figure 2b shows the best fit estimate for the model parameters. The corresponding estimated values of the parameters in non-dimensional form are respectively  $\alpha_1 = 5786.32$ ,  $\alpha_2 = 566.968$  and  $\eta_2 = 0.2963$ .

We repeat these processes with five sets of data with different intensity of noises and succeeded in getting a range of values in which the parameters  $\beta_1, \beta_2$  and  $\mu_2$  lies. All the values of the system parameters are given in tabular form in Table 1.

#### 4 Analysis of the System

To reduce the number of the system parameters and for numerical simulations, we non-dimensionalize the system using the following scaling,

$$x = \frac{L}{K_1}, y = \frac{P}{K_1}, z = \frac{A}{K_2}, w = \frac{T}{K_2}, t = rt_1, a = \frac{a_1}{r}, b = \frac{b_1}{r}, \eta_1 = \frac{\mu_1}{r},$$

$$\eta_2 = \frac{\mu_2}{r}, k_1 = \frac{r_1 K_1}{r K_2}, k_2 = \frac{r_2 K_1}{r K_2}, \alpha_1 = \frac{\beta_1 K_2}{r}, \alpha_2 = \frac{\beta_2 K_2}{r}.$$

Then the system can be described as

$$\frac{dx}{dt} = aux(1 - x) - b(1 - u)x, \quad (5)$$

$$\frac{dy}{dt} = b(1 - u)x - \eta_1 y, \quad (6)$$

$$\frac{dz}{dt} = k_1 x + k_2 y - \eta_2 z - \alpha_1 zw, \quad (7)$$

$$\frac{dw}{dt} = w(1 - w) - \alpha_2 zw, \quad (8)$$



with initial conditions  $x(0) = x_0$ ,  $y(0) = y_0$ ,  $z(0) = z_0$  and  $w(0) = w_0$ . It can easily be shown that the right hand sides of system (5–8) are continuous and satisfy Lipschitz condition in  $\mathbb{R}_+^4$ .

#### 4.1 Positivity and Boundedness of Solution

Throughout this paper we denote  $q_0 := au - b(1 - u)$  and assume that it is positive.

**Theorem 1** *Let the initial conditions of system (5–8) be positive. Then the solutions  $(x(t), y(t), z(t), w(t))$  of system are non-negative for all  $t \geq 0$ .*

**Theorem 2** *The solutions of system (5–8) with non negative initial conditions are bounded.*

Proof: From equations (5) and (6), we have

$$\begin{aligned} \frac{d}{dt}(x + y) &= aux(1 - x) - \eta_1 y \\ &= \frac{(\eta_1 + au)^2}{4au} - \eta_1(x + y) - au\left(x - \frac{\eta_1 + au}{2au}\right)^2 \\ &\leq \frac{(\eta_1 + au)^2}{4au} - \eta_1(x + y). \end{aligned}$$

Hence, using standard differential inequalities, we have  $x + y \leq \frac{(\eta_1 + au)^2}{4au\eta_1}$ .

Similarly, from equations (7) and (8), since  $x(t) + y(t)$  is bounded (say by  $k_0$ ), we have

$$\begin{aligned} \frac{d}{dt}(z + w) &= k_1 x + k_2 y - \eta_2 z + w(1 - w) - (\alpha_1 + \alpha_2)zw \\ &\leq k_2(x + y) - \eta_2(z + w) - \left(w - \frac{1 + \eta_2}{2}\right)^2 + \frac{(1 + \eta_2)^2}{4} \\ &\leq k_2 k_0 + \frac{(1 + \eta_2)^2}{4} - \eta_2(z + w). \end{aligned}$$

Hence  $(z + w) \leq \frac{k_2 k_0}{\eta_2} + \frac{(1 + \eta_2)^2}{4\eta_2}$ . Therefore, the solutions of system (5–8) are bounded.

#### 4.2 Equilibria and Local Stability Analysis

The equilibrium points of system (5–8) are  $E_0 = (0, 0, 0, 0)$ ,  $E_1 = (0, 0, 0, 1)$ ,  $E_2 = (\bar{x}, \bar{y}, \bar{z}, 0)$  and  $E^* = (\bar{x}, \bar{y}, z^*, w^*)$ , where  $\bar{x} = \frac{au-b(1-u)}{au}$ ,  $\bar{y} = \frac{b(1-u)\bar{x}}{\eta_1}$ ,  $\bar{z} = \frac{k_1\bar{x}+k_2\bar{y}}{\eta_2}$  and  $w^* = 1 - \alpha_2 z^*$  such that  $z^*$  is the positive roots of the quadratic equation

$$\alpha_1 \alpha_2 z^2 - (\alpha_1 + \eta_2)z + (k_1 \bar{x} + k_2 \bar{y}) = 0. \quad (9)$$

**Note:** If  $q_0 = au - b(1 - u) < 0$  then the cancerous cells free  $E_2$  and the positive interior  $E^*$  equilibrium points of the system will not exist. But, from the linear stability analysis one can show that the equilibrium point  $E_0$  is unstable and the equilibrium point  $E_1$  is stable.

We now study the linear stability of the cancerous cells free and the positive interior equilibrium points system (5 – 8). The jacobian matrix  $J_{E_2}$  at the boundary equilibrium point  $E_2$  is given by

$$J_{E_2} = \begin{pmatrix} -(au - b(1 - u)) & 0 & 0 & 0 \\ b(1 - u) & -\eta_1 & 0 & 0 \\ k_1 & k_2 & -\eta_2 & -\alpha_1 \bar{z} \\ 0 & 0 & 0 & 1 - \alpha_2 \bar{z} \end{pmatrix}$$

and the corresponding characteristic equation is

$$(\lambda + au - b(1 - u))(\lambda + \eta_1)(\lambda + \eta_2)(\lambda - (1 - \alpha_2 \bar{z})) = 0. \quad (10)$$

Therefore, the equilibrium point  $E_2$  (the cancerous cells free equilibrium point) is locally asymptotically stable (LAS) if  $1 - \alpha_2 \bar{z} < 0$ .

The Jacobian matrix  $J_{E^*}$  at the interior equilibrium point  $E^*$  is given by

$$J_{E^*} = \begin{pmatrix} -(au - b(1 - u)) & 0 & 0 & 0 \\ b(1 - u) & -\eta_1 & 0 & 0 \\ k_1 & k_2 & -\eta_2 - \alpha_1 w^* & -\alpha_1 z^* \\ 0 & 0 & -\alpha_2 w^* & -w^* \end{pmatrix}$$

Then, the corresponding characteristic equation is

$$(\lambda + au - b(1 - u))(\lambda + \eta_1)[\lambda^2 + (\eta_3 + w^*(1 + \alpha_1))\lambda + w^*(\eta_2 + \alpha_1 - 2\alpha_1\alpha_2z^*)] = 0 \quad (11)$$

**Theorem 3** *Let  $z_+^*$  and  $z_-^*$  be roots equation (6). The interior equilibrium point  $E_-^* = (\bar{x}, \bar{y}, z_-^*, w^*)$ , (the high number of cancerous cells equilibrium point) is LAS when ever it exists and  $E_+^* = (\bar{x}, \bar{y}, z_+^*, w^*)$  is unstable.*

Proof: From the characteristic equation (11) the equilibrium point  $E^*$  is LAS provided that the roots of the quadratic equation

$$\lambda^2 + (\eta_2 + w^*(1 + \alpha_1))\lambda + w^*(\eta_2 + \alpha_1 - 2\alpha_1\alpha_2z^*) = 0, \quad (12)$$

are negative or with negative real parts. But from (9) we have,

$$\eta_2 + \alpha_1 - 2\alpha_1\alpha_2z^* = \mp \sqrt{(\eta_2 + \alpha_1)^2 - 4\alpha_1\alpha_2(k_1\bar{x} + k_2\bar{y})}$$

Hence, the roots of equation (11) are negative or with negative real parts if  $\eta_2 + \alpha_1 - 2\alpha_1\alpha_2z^* > 0$ . Therefore,  $E_-^* = (\bar{x}, \bar{y}, z_-^*, w^*)$  is LAS and  $E_+^* = (\bar{x}, \bar{y}, z_+^*, w^*)$  is unstable.

#### 4.3 Global Stability Analysis

We now study the global stability of  $E_2$ , the cancerous cells free equilibrium point and  $E_-^*$ , the high number of cancerous cells equilibrium point.

**Theorem 4** *The cancerous cells free equilibrium point  $E_2$  is globally asymptotically stable if  $\alpha_2 > \frac{(\alpha_1 + \eta_2)^2}{4\alpha_1(k_1\bar{x} + k_2\bar{y})}$ .*

Proof: One can easily show that

$$\frac{\eta_2}{k_1\bar{x} + k_2\bar{y}} < \frac{(\alpha_1 + \eta_2)^2}{4\alpha_1(k_1\bar{x} + k_2\bar{y})}.$$

Then,  $\alpha_2 > \frac{(\alpha_1 + \eta_2)^2}{4\alpha_1(k_1\bar{x} + k_2\bar{y})}$  implies that  $1 - \alpha_2\bar{z} < 0$ . Hence the cancerous cells free equilibrium point  $E_2$  is LAS. From equation (5) we have

$$x(t) = \frac{q_0}{au(1 - ce^{-q_0t})}, \text{ where } c = 1 - \frac{q_0}{aux_0}.$$

Hence,  $\lim_{t \rightarrow \infty} x(t) = \frac{au-b(1-u)}{au} = \bar{x}$ . From the definition of limit superior, for any  $\epsilon > 0$ , we have

$$\frac{dy}{dt} = b(1-u)x - \eta_1 y \leq b(1-u)(\bar{x} - \epsilon) - \eta_1 y.$$

Hence,

$$\limsup_{t \rightarrow \infty} y(t) \leq \frac{b(1-u)\bar{x}}{\eta_1} = \bar{y}, \quad (\text{since } \epsilon \text{ is arbitrarily small}).$$

Similarly using the definition of limit inferior one can show that

$$\liminf_{t \rightarrow \infty} y(t) \geq \frac{b(1-u)\bar{x}}{\eta_1} = \bar{y}.$$

Therefore,  $\lim_{t \rightarrow \infty} y(t) = \frac{b(1-u)\bar{x}}{\eta_1} = \bar{y}$ . On the other hand, from equation (7) and using the definition of limit superior, for  $\epsilon > 0$ , we have

$$\begin{aligned} \frac{dz}{dt} &= k_1 x + k_2 y - \eta_2 z - \alpha_1 z w, \\ &\leq k_1 x + k_2 y - \eta_2 z, \\ &\leq \eta_2 \left( \frac{k_1 \bar{x} + k_2 \bar{y}}{\eta_2} - z \right). \end{aligned}$$

$$\text{Therefore, } \limsup_{t \rightarrow \infty} z(t) \leq \frac{k_1 \bar{x} + k_2 \bar{y}}{\eta_2} = \bar{z}.$$

Thus, for every  $\epsilon > 0$ , there exist a time  $T_1$  such that  $z(t) \geq (\bar{z} - \epsilon)$  for  $t \geq T_1$ . Using this inequality in the equation (8) we have,

$$\frac{dw}{dt} = w(1 - \alpha_2 z - w) \leq w(1 - \alpha_2(\bar{z} - \epsilon) - w)$$

Since  $\epsilon$  is arbitrarily small and  $w(t)$  is non negative for all  $t > 0$ , we have,  $\limsup_{t \rightarrow \infty} w(t) = 0$ . Therefore, for  $\alpha_2 > \frac{(\alpha_1 + \eta_2)^2}{4\alpha_1(k_1 \bar{x} + k_2 \bar{y})}$ , the cancerous cell free equilibrium point  $E_2 = (\bar{x}, \bar{y}, \bar{z}, 0)$  is globally asymptotically stable.

**Theorem 5** *The positive interior equilibrium point  $E_-^*$  is globally asymptotically stable if  $(1 - \alpha_2 \bar{z}) > 0$ .*

Proof: For  $0 < \alpha_2 < \frac{1}{\bar{z}}$ , the equilibrium point  $E_-^*$  is LAS. From theorem (4), we have  $\lim_{t \rightarrow \infty} x(t) = \bar{x}$ ,  $\lim_{t \rightarrow \infty} y(t) = \bar{y}$  and  $\frac{dw}{dt} \leq w(1 - \alpha_2(\bar{z} - \epsilon) - w)$ . Then,  $\limsup_{t \rightarrow \infty} w(t) \leq (1 - \alpha_2(\bar{z} - \epsilon))$ , if  $(1 - \alpha_2(\bar{z} - \epsilon)) > 0$ . But since  $\epsilon > 0$  is arbitrarily small, we have  $\limsup_{t \rightarrow \infty} w(t) \leq (1 - \alpha_2\bar{z}) =: w_0^*$ , provided that  $(1 - \alpha_2\bar{z}) > 0$ . From the definition of limit superior, for every  $\epsilon > 0$ ,  $w(t) \leq (w_0^* + \epsilon)$  for all  $t > 0$ . Substituting this in equation (7) we get

$$\begin{aligned} \frac{dz}{dt} &\geq k_1\bar{x} + k_2\bar{y} - (\eta_2 + \alpha_1(w_0^* + \epsilon))z \\ &= (\eta_2 + \alpha_1(w_0^* + \epsilon))\left(\frac{k_1\bar{x} + k_2\bar{y}}{\eta_2 + \alpha_1(w_0^* + \epsilon)} - z\right). \end{aligned}$$

Then, using differential inequality we have

$$\liminf_{t \rightarrow \infty} z(t) \geq \frac{k_1\bar{x} + k_2\bar{y}}{\eta_2 + \alpha_1(w_0^* + \epsilon)}.$$

Since,  $\epsilon > 0$  is arbitrarily small, we have

$$\liminf_{t \rightarrow \infty} z(t) \geq \frac{k_1\bar{x} + k_2\bar{y}}{\eta_2 + \alpha_1 w_0^*} =: z_0^*.$$

From the definition of limit inferior, for every  $\epsilon > 0$ , there exist a time  $T_2$  such that  $z \leq z_0^* + \epsilon$  for all  $t \geq T_2$ . Substituting this inequality in equation of (8) once again we get the inequality  $\frac{dw}{dt} \geq w(1 - \alpha_2(z_0^* + \epsilon) - w)$ , which intern implies that

$$\liminf_{t \rightarrow \infty} w(t) \geq 1 - \alpha_2 z_0^* =: w^*$$

as  $\epsilon > 0$  is arbitrarily small. From the definition of limit inferior, for every  $\epsilon > 0$ ,  $w \geq w^* - \epsilon$  for all  $t > 0$ . Therefore,

$$\frac{dz}{dt} \leq (\eta_2 + \alpha_1(w^* - \epsilon))\left(\frac{k_1\bar{x} + k_2\bar{y}}{\eta_2 + \alpha_1(w^* - \epsilon)} - z\right)$$

and hence

$$\limsup_{t \rightarrow \infty} z(t) \leq \frac{k_1\bar{x} + k_2\bar{y}}{\eta_2 + \alpha_1 w^*} =: z^*,$$

since again as  $\epsilon > 0$  is so small. From the definition of limit superior again, for every  $\epsilon > 0$ , we have  $z \geq z^* - \epsilon$  for all  $t > 0$ . Substituting this inequality in

equation (8), we get  $\frac{dw}{dt} \leq w(1 - \alpha_2(z^* - \epsilon) - w)$  and hence  $\limsup_{t \rightarrow \infty} w(t) \leq 1 - \alpha_2 z^* =: w^*$ , as  $\epsilon$  is arbitrarily small. Now

$$\begin{aligned}
\limsup_{t \rightarrow \infty} z(t) - \liminf_{t \rightarrow \infty} z(t) &= z^* - z_0^* \\
&= \frac{k_1 \bar{x} + k_2 \bar{y}}{\eta_2 + \alpha_1 w^*} - \frac{k_1 \bar{x} + k_2 \bar{y}}{\eta_2 + \alpha_1 w_0^*} \\
&= \frac{\alpha_1(k_1 \bar{x} + k_2 \bar{y})}{(\eta_2 + \alpha_1 w^*)(\eta_2 + \alpha_1 w_0^*)} (w_0^* - w^*) \\
&= \frac{\alpha_2 \alpha_1 (k_1 \bar{x} + k_2 \bar{y})}{(\eta_2 + \alpha_1 w_0^*)(\eta_2 + \alpha_1 w^*)} (z_0^* - z_0) \\
&= \frac{\alpha_2 \alpha_1^2 (k_1 \bar{x} + k_2 \bar{y})^2}{\eta_2 (\eta_2 + \alpha_1 w_0^*)^2 (\eta_2 + \alpha_1 w^*)} (-w_0^*) < 0,
\end{aligned}$$

which is a contradiction since  $w_0^* = 1 - \alpha_2 \bar{z} > 0$ . Therefore,

$\limsup_{t \rightarrow \infty} z(t) = \liminf_{t \rightarrow \infty} z(t) = z^*$ . Similarly,

$\limsup_{t \rightarrow \infty} w(t) - \liminf_{t \rightarrow \infty} w(t) = w_0^* - w^* = \alpha_2(z_0^* - z^*) < 0$ , which is again a contradiction. Therefore,

$$\lim_{t \rightarrow \infty} (x(t), y(t), z(t), w(t)) = (\bar{x}, \bar{y}, z^*, w^*),$$

and hence the positive interior equilibrium point  $E_-^* = (\bar{x}, \bar{y}, z^*, w^*)$  is globally asymptotically stable.

#### 4.4 Bifurcation Analysis

In this section, we explore the critical parameter values where the qualitative behavior of the system changes. By using the Dulac-Bendixson theorem, one can show that system (5 – 8) has no closed orbit for positive solutions. Equations (5) and (6) can be evaluated analytically as,

$$\begin{aligned}
x(t) &= \frac{q_0}{au(1 - ce^{-q_0 t})}, \text{ where } c = 1 - \frac{q_0}{aux_0} \\
y(t) &= y_0 e^{-\eta_1 t} + b(1 - u) \int_0^t e^{\eta_1(s-t)} x(s) ds,
\end{aligned}$$

which are not closed orbits. To show that the other solutions are also not a closed orbit, we consider the function  $m(w, z) = \frac{1}{wz}$ . Then

$$\begin{aligned}
L &= \frac{\partial}{\partial z}(m(w, z)\frac{dz}{dt}) + \frac{\partial}{\partial w}(m(w, z)\frac{dw}{dt}) \\
&= \frac{\partial}{\partial z}\left(\frac{1}{wz}(k_1x + k_2y - \eta_2z - \alpha_1zw)\right) + \frac{\partial}{\partial w}\left(\frac{1}{wz}(w(1-w) - \alpha_2zw)\right) \\
&= -\frac{1}{z}\left(\frac{k_1x + k_2y}{wz} + 1\right).
\end{aligned}$$

Since all the parameter values are positive,  $L < 0$  over the domain of interest and hence the system satisfies the Dulac-Bendixson theorem. Therefore, there are no limit cycles or homoclinic connections for the system. Similarly, from the values of the eigenvalues of the corresponding Jacobian matrix, there are no Hopf bifurcations, which may give rise to the occurrence of limit cycles.

The system has different steady states depending on the values of the system parameters. The equilibrium points  $E_0 = (0, 0, 0, 0)$  and  $E_1 = (0, 0, 0, 1)$  exist for all parameter values. The cancerous cells free steady state  $E_2 = (\bar{x}, \bar{y}, \bar{z}, 0)$  exists if  $au - b(1 - u) > 0$ . The other two positive steady states  $E^*$  exist under the following conditions:

- (i) Let  $\alpha_1 - \eta_2 > 0$ . The equilibrium point  $E_+^*$  exist if  $\frac{1}{\bar{z}} < \alpha_2 < \frac{(\alpha_1 + \eta_2)^2}{4\alpha_1(k_1\bar{x} + k_2\bar{y})}$ , and the equilibrium point  $E_-^*$  exist if  $\alpha_2 < \frac{(\alpha_1 + \eta_2)^2}{4\alpha_1(k_1\bar{x} + k_2\bar{y})}$ .
- (ii) Let  $\alpha_1 - \eta_2 < 0$ . The equilibrium point  $E_-^*$  exists if  $\alpha_2 < \frac{1}{\bar{z}}$ .

All these situations are sketched in fig.3.

The stability of the cancerous cells free equilibrium point  $E_2$  changes as the value of the parameter  $\alpha_2$  passes through the critical value  $\alpha_{21} = \frac{1}{\bar{z}} = \frac{\eta_2}{(k_1\bar{x} + k_2\bar{y})}$ . Hence  $\alpha_2$ , which represents the effectiveness of the antibodies to destroy the cancerous cells, is the bifurcation parameter for the system. The Jacobian matrix  $J$  at  $E_2$  and its transpose have a simple eigenvalue  $\lambda = 0$  with corresponding eigenvector  $\mathbf{v}^T = (0, 0, -\frac{\alpha_1\bar{z}}{\eta_2}, 1)$  and  $\mathbf{w}^T = (0, 0, 0, 1)$  respectively at the bifurcation parameter value  $\alpha_2 = \frac{1}{\bar{z}}$ . If  $\mathbf{f}_{\alpha_2}$  denote the vector of partial derivatives of the components of the right hand side of system (5 – 8) with respect to the scalar  $\alpha_2$  and  $D\mathbf{f}(E_2, \alpha_2)\mathbf{v}$  is the directional derivative of  $\mathbf{f}$  in the direction of  $\mathbf{v}$  at the equilibrium point  $E_2$ , then,

$$\begin{aligned}
\mathbf{w}^T \mathbf{f}_{\alpha_2}(E_2) &= 0, \mathbf{w}^T [D\mathbf{f}_{\alpha_2}(E_2, \alpha_{21})\mathbf{v}] = -\frac{\bar{z}}{\|\mathbf{v}\|} = -\frac{1}{\alpha_2 \|\mathbf{v}\|}, \text{ and} \\
\mathbf{w}^T [D^2\mathbf{f}(E_2, \alpha_{21})(\mathbf{v}, \mathbf{v})] &= \frac{2(\alpha_1 - \eta_2)}{\eta_2 \|\mathbf{v}\|^2},
\end{aligned}$$

which are non-zero for  $\alpha_1 - \eta_2 \neq 0$ . Therefore, by Sotomayor theorem [35], the system experiences transcritical bifurcation at the cancerous cells free

equilibrium point  $E_2 = (\bar{x}, \bar{y}, \bar{z}, 0)$ , as the parameter  $\alpha_2$  passes through the bifurcation parameter value  $\alpha_2 = \alpha_{21} = \frac{1}{\bar{z}}$ .

Again, as the value of  $\alpha_2$  passes through the critical value  $\alpha_2 = \alpha_{22} = \frac{(\alpha_1 + \eta_2^2)}{4\alpha_1(k_1\bar{x} + k_2\bar{y})}$ , the number of positive interior equilibrium points of the system changes. As the value of  $\alpha_2$  passes through the critical value  $\alpha_{22}$ , the positive interior equilibrium points  $E_+^*$  and  $E_-^*$  collide and disappear. At the critical value of  $\alpha_2 = \alpha_{22}$  the system has new interior equilibrium point  $E_* = (\bar{x}, \bar{y}, \frac{\alpha_1 + \eta_2}{2\alpha_1\alpha_2}, \frac{\alpha_1 - \eta_2}{2\alpha_1})$ , provided  $\alpha_1 - \eta_2 > 0$ . Then the Jacobian matrix  $J$  at  $E_*$  and its transpose has a simple eigenvalue  $\lambda = 0$  with corresponding eigenvectors  $\mathbf{v}^T = (0, 0, -\frac{1}{\alpha_2}, 1)$  and  $\mathbf{w}^T = (-\frac{\alpha_2(b(1-u)k_2 + \eta_1k_1)(\alpha_1 - \eta_2)}{\alpha_1\eta_1q_0(\alpha_1 + \eta_2)}, -\frac{\alpha_2k_2(\alpha_1 - \eta_2)}{\alpha_1\eta_1(\alpha_1 + \eta_2)}, \alpha_2(\frac{1}{\alpha_1} - \frac{2}{\alpha_1 + \eta_2}), 1)$  respectively, corresponding to the eigenvalue  $\lambda = 0$  at the critical value  $\alpha_2 = \alpha_{22}$ . Then,

$$\mathbf{w}^T \mathbf{f}_{\alpha_2}(E_*, \alpha_{22}) = -\frac{(\alpha_1 + \eta_2)(\alpha_1 - \eta_2)}{4\alpha_2\alpha_1^2}, \text{ and}$$

$$\mathbf{w}^T [D^2(\mathbf{f}(E_*, \alpha_{22}))(\mathbf{v}, \mathbf{v})] = \frac{4\eta_2}{(\alpha_1 + \eta_2)\|\mathbf{v}\|^2},$$

which are non-zero for  $\alpha_1 \neq \eta_2$ . Therefore, by Sotomayor theorem, there is a smooth curve of the equilibrium point of the system in  $\mathbb{R}^4 \times \mathbb{R}$  passing through the point  $(E_*, \alpha_{22})$  and tangent to the hyper plane  $\mathbb{R}_+^4 \times \alpha_{22}$ . Hence, the system has a saddle-node bifurcation as the parameter  $\alpha_2$  passes through the critical bifurcation parameter value  $\alpha_2 = \alpha_{22}$ .

## 5 Numerical Results and Biological Implications

In this section we present the numerical results of system (5 – 8) for the parameter values given in Table 1. The steady state  $E_0 = (0, 0, 0, 0)$  and  $E_1 = (0, 0, 0, 1)$  exist for the parameter values given in Table 1. The cancerous cells free equilibrium point  $E_2 = (\bar{x}, \bar{y}, \bar{z}, 0)$  exists for the system parameters provided that  $au > b(1 - u)$ , which holds true for the parameter values given in Table 1. If  $\alpha_{21} = 0.227538 < \alpha_2 < \alpha_{22} = 1111.032892$ , the positive interior equilibrium points  $E_+^*$ , characterized by relatively low number of cancerous cells and  $E_-^*$ , characterized by relatively high number of cancerous cells exist keeping the other parameter values fixed. For  $0 < \alpha_2 < \alpha_{21} = 0.227538$ , only the high number of cancerous cells equilibrium point  $E_-^*$  exists. As the value of  $\alpha_2$  increases and passes through the critical value  $\alpha_{22} = 1111.032892$ , the equilibrium points  $E_+^*$  and  $E_-^*$  collide and disappear.

By linearizing the system about the steady states, the stability of the equilibrium points are determined, which is important from physiological point



of view. From the linear stability analysis we have seen that, the equilibrium points  $E_0 = (0, 0, 0, 0)$  and  $E_1 = (0, 0, 0, 1)$  are unstable for  $au - b(1 - u) > 0$  and the cancerous cells free equilibrium point  $E_2$  is stable if  $1 - \alpha_2 \bar{z} < 0$ , that is,  $\alpha_2 > \frac{1}{\bar{z}} = 0.227538$  and unstable otherwise. The stability of  $E_2$  implies that the antibodies can clear the cancerous cells. As  $\alpha_2$  passes through the critical value  $\alpha_{21} = 0.227538$ , the stability of  $E_2$  changes from unstable to stable and hence the system has a transcritical bifurcation at this point. Using the software **Matcont**, the point at which the system experiences transcritical bifurcation is  $BP = (0.550000 \ 0.495000 \ 4.394869 \ 0.000000 \ 0.227538)$ , where  $x = 0.55$ ,  $y = 0.495$ ,  $z = 4.394869$ ,  $w = 0.00$  and  $\alpha_2 = \alpha_{21} = 0.227538$ . As the value of  $\alpha_2$  passes through the critical value  $\alpha_{22} = 1111.032892$  the two positive interior equilibrium points collide and disappear, where the system experiences a saddle node bifurcation at this point. Using **Matcont**, the point at which the system experiences the saddle node bifurcation is given by  $LP = (0.550000 \ 0.495000 \ 0.000450 \ 0.499974 \ 1111.032892)$ , where  $x=0.55$ ,  $y=0.495$ ,  $z=0.000450$ ,  $w=0.499974$  and  $\alpha_2 = \alpha_{22} = 1111.032892$ . This is shown in fig.4a and 4b, where BP is the branching point, LP is the limit point and H is the neutral saddle, which has no meaning in the biological context. Also, it has been shown that  $E_2$  attains global stability provided that  $\alpha_2 > \alpha_{22}$ .

The high number of cancerous cells equilibrium point  $E_-^*$  is stable whenever it exists and  $E_+^*$  is unstable always. In the region  $0 < \alpha_2 < \alpha_{21}$ , the high number of cancerous cells equilibrium point is the only stable (globally stable) equilibrium point of the system and hence the cancerous cells succeed to survive. This is depicted in fig.5, which implies that the cancerous cells will escape immune surveillance unless each and every cancerous cells are killed, that is, the system will ineluctably return to the high-cancer state if the treatment is stopped. Thus, in order to realistically effect a cure when the cancer free equilibrium point is unstable, a therapy or treatment must ensure that not only the cancer burden must be reduced but the therapy itself is capable of changing the parameter values of the system. In this context, monoclonal antibody therapy of cancer [36] is suggested as treatment, which may be capable of changing the system parameters. Monoclonal antibodies (MAbs) can be used to target a number of cancer associated targets, including tumor associated blood vessels, vascular growth factors, diffuse malignant cells like leukemia, cancerous cells with a solid tumor and tumor associated stroma like fibroblasts.

If  $\alpha_{21} < \alpha_2 < \alpha_{22}$ , then both the cancerous cells free equilibrium  $E_2$  and the high number of cancerous cells equilibrium  $E_-^*$  are stable, that is, this region is the region of bistability. In this region, the system is sensitive to the initial conditions and some parameter values. Depending on the initial conditions and some of the values of the system parameters given in Table 1, a given initial value of the cancerous cell will either grow to the stable high number of cancerous cells equilibrium point  $E_-^*$  (the cancerous cells succeed to survive) or decays to the cancerous cells free equilibrium point  $E_2$  (the immune system

succeeds in eradicating the cancerous cells). Fig.6 captures the dynamics of the sensitivity of the system with respect to the initial conditions. The sensitivity of the system on the parameter  $\alpha_2$  is shown in fig.7.

As the value of  $\alpha_2$  increases towards the critical value  $\alpha_{22}$ , the quantity of the high number of cancerous cells equilibrium point decreases to about half the carrying capacity  $K_2$  of the cancerous cells. When the value of  $\alpha_2$  increases and exceeds the critical value  $\alpha_{22}$ , any amount of cancerous cells decays to zero after some time, that is, the immune system succeed in clearing the cancerous cells. The time at which a given amount of cancerous cells drops to zero depends on the initial conditions and some values of system parameters. When  $\alpha_2 > \alpha_{22}$ , there is only cancer free equilibrium and it is stable. Fig.8 shows, once the critical point  $\alpha_{22}$  is crossed, the cancerous cells always decays to zero, no matter what the initial values are.

As stated earlier, the effect of monoclonal therapy, which is capable of changing the system parameter, is evidently visible in this region, that is, when  $\alpha_2 > \alpha_{22}$ . In this therapy, a monoclonal antibody can be directed to attach to certain cancerous cells. Cetuximab (Erbiximab), a monoclonal antibody approved to treat colon cancer and head and neck cancers, attaches to receptors on cancer cells that accept a certain growth signal (epidermal growth factor). Cancer cells and some healthy cells rely on this signal to tell them to divide and multiply. Blocking this signal from reaching its target on the cancerous cells may slow or stop the cancer from growing. There are a number of monoclonal antibody drugs that are available to treat various types of cancer by (a) making the cancerous cells more visible to the immune system (b) delivering radiation to cancerous cells (c) slipping powerful drugs into cancerous cells. Recent clinical investigations show that they are capable of killing cancerous cells directly [1]. However, more clinical trials are necessary before it comes out in the form of medicine to mimic that effect.

## 6 Conclusion

In this paper, we have formulated a system of non-linear ordinary differential equations that describes the stimulatory effect of cancerous cells on immune cells in conjunction with antibodies. The model we have proposed is simple and more of general type. The major difference of our model from that of the existing literature in this direction is that the immune system we considered here is antibody mediated T-cell independent immune responses. In this dynamics, a significant role is played by  $\alpha_2$ , the effectiveness of the antibodies to kill the cancerous cells directly.

From our study we observe that for certain values of  $\alpha_2$ , one can control the

unlimited growth of the cancerous cells. From the analysis of our model, we determine some criterion for the existence of the equilibrium points of the system and the stability conditions. For a specific set of parameter values, we obtain five equilibrium points, namely, the zero equilibrium point  $E_0$ , the boundary equilibrium point  $E_1$ , the cancer-free equilibrium point  $E_2$  and two positive interior equilibrium points  $E^*$ . Initially, the cancerous cells free equilibrium point was unstable and the high number of cancerous cell equilibrium point was stable ( $\alpha_2 < \alpha_{21}$ ). This means any treatment to be effective, it must have the ability to change the system parameter and force this desirable equilibrium point to become stable.

On the other hand, the stability of the high number of cancerous cells equilibrium point implies that reducing the cancer burden through any effective treatment is not sufficient enough to kill all the cancerous cells. Once the treatment stops, the system, even with an untraceable sign of cancer, will return to high number of cancerous cells state. However, alteration of system parameters through monoclonal antibody therapy of cancer, may have the ability to change the stability nature of the cancer free equilibrium point and allowing a new treatment protocol to eradicate cancerous cells. In fact, it has been tested clinically that monoclonal antibodies directed to CD20 and HLA-DR can elicit homotypic adhesion followed by lysosome-mediated cell death in human lymphoma and leukemia cells [36]. In the stability analysis of our model, we obtain a region of bi-stability and observe that the growth of the cancerous cells can be controlled and reduced at early stage of its growth by enhancing the patient's own defense mechanism, that is, the antibodies to fight against the cancerous cells.

We perform bifurcation analysis of the system for the parameter  $\alpha_2$ , which represents the effectiveness of antibodies to eliminate cancerous cells. From the analysis, we observed that for certain parameter values of the system, the long term behavior of the system can be sensitive to the initial number of the cancerous cells. In the region where there is bi-stability (the stability region of both the cancer free and high number of cancerous cells equilibrium points), for the cancerous cell population that are very close to the boundary separating the region of attraction of these equilibrium points, a slight change in the initial conditions will change the behavior of the system. One important implication of this result for the treatment of cancer is that if both the cancer-free and high number of cancerous cells equilibria are stable, then for cancerous cell population that are close to the boundary separating the basins of attraction of these equilibria, very small changes in the initial number of cancerous cells can have drastic consequences on the outcome of the cure. Therefore, by determining some of the values of the system parameters, we can achieve the stable cancerous cells free equilibrium point to cure the disease. At the end we would like to mention that the model can be modified further by adding delay terms, diffusive terms and stochastic fluctuations to the system to bring

out more rich dynamics of the system, which we propose as our future work.

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Table 1

**Parameter values used for numerical illustration**

Parameters	Values	Scaled	References
$a_1$ (the growth rate of large B-cells)	$(0.02 - 0.2) \text{ hr.}^{-1}$	0.0464 -0.464	[5]
$b_1$ (the conversion rate of large b-cells into plasma cells)	$0.01 \text{ hr.}^{-1}$	0.0232	[5]
$\mu_1$ (the natural death rate of plasma cells)	$(0.002 - 0.02) \text{ hr.}^{-1}$	0.00464-0.0464	[5]
$K_1$ (the carrying capacity of large B-cells)	$10^6 \text{ cells}$	—	[5]
$u$ (the fraction of daughter cells which remain as large B-cells)	0.1	—	[5]
$r_1$ (the rate at which large B-cells secrete antibodies)	$100 \text{ Ab cell}^{-1} \text{ sec.}^{-1}$	0.236754	[29,30,31]
$r_2$ (the rate at which plasma cells secrete antibodies)	$1000 \text{ Ab cell}^{-1} \text{ sec.}^{-1}$	2.36754	[29,30,31]
$\mu_2$ (the natural death rate of antibodies)	$0.1277 - 0.6465 \text{ sec.}^{-1}$	0.2963 - 1.5	estimated
$\beta_1$ (the death rate of antibodies due to interaction with cancerous cells)	$6.0436 \times 10^{-9} - 2.5448 \times 10^{-6} \text{ cell}^{-1} \text{ hr.}^{-1}$	13.7418 -5786.32	estimated
$r$ (the intrinsic growth rate of cancerous cells)	$0.431 \text{ day}^{-1}$	—	[33]
$K_2$ (the carrying capacity of cancerous cells)	$9.8 \times 10^8 \text{ cells}$	—	[33]
$\beta_2$ (the death rate of cancerous cells due to interaction with antibodies)	$9.0135 \times 10^{-10} - 2.4935 \times 10^{-7} \text{ Ab}^{-1} \text{ hr.}^{-1}$	2.05 - 566.968	estimated

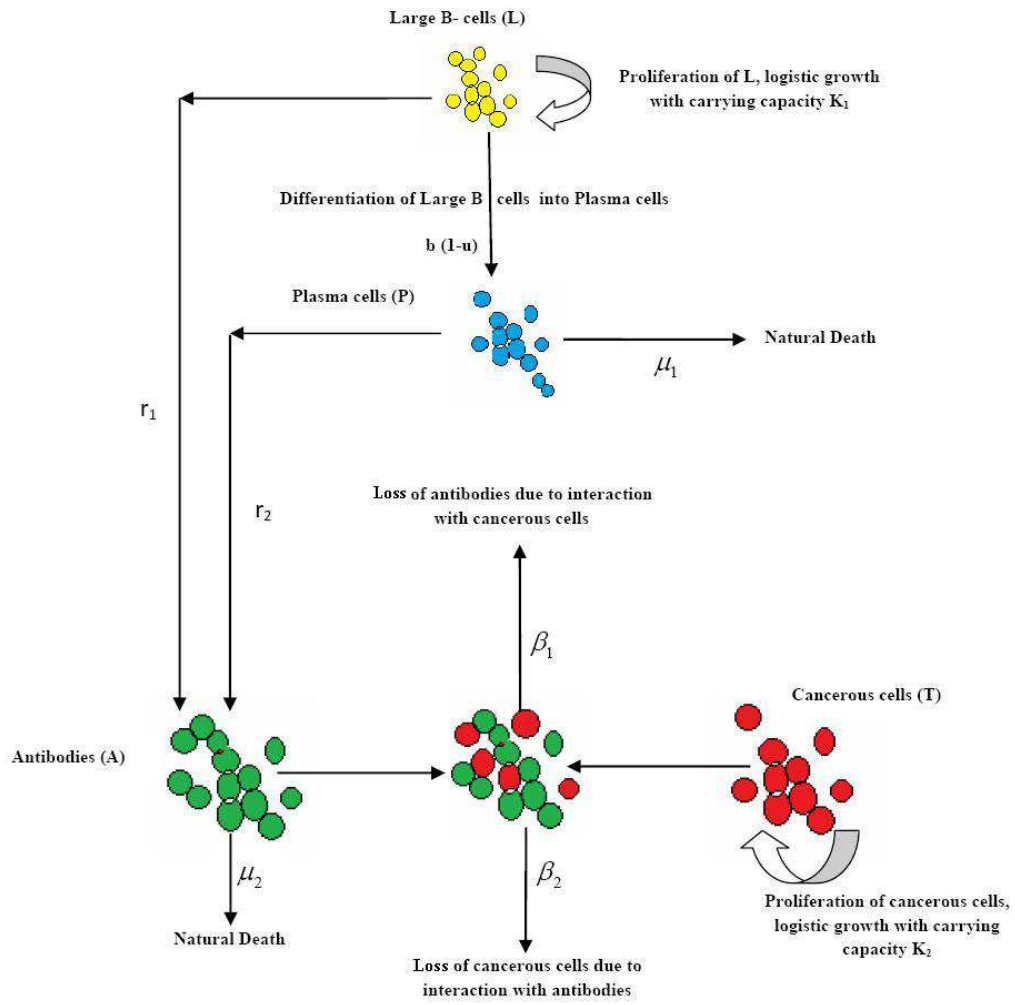


Fig. 1. The schematic diagram illustrates the interaction between large B-cells, plasma cells, antibodies and the cancerous cells



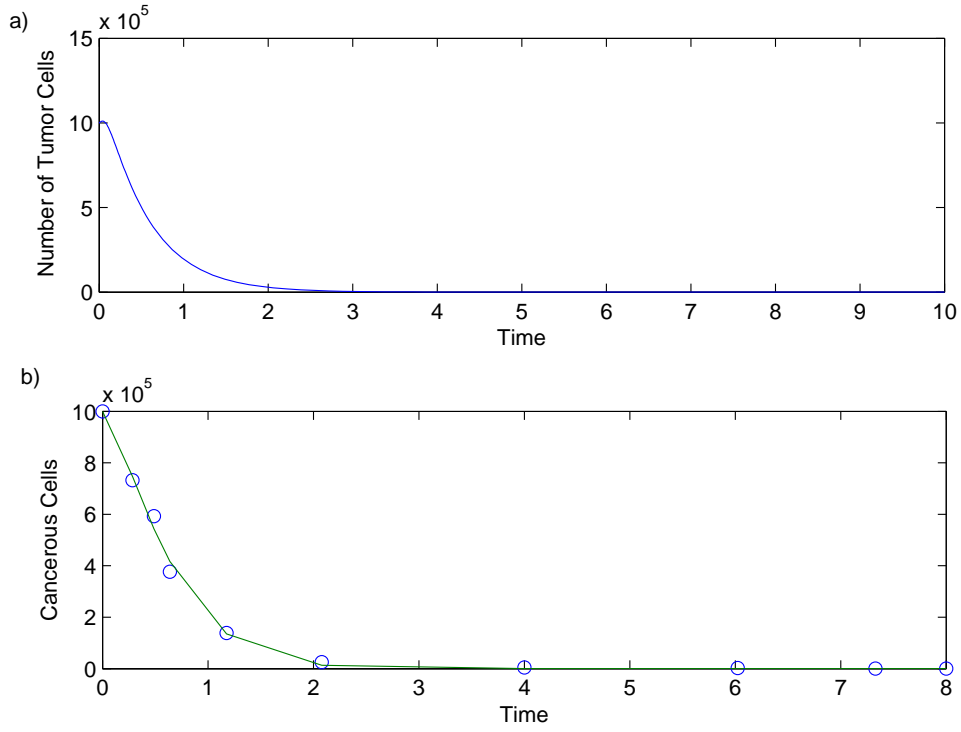


Fig. 2. The figure shows how syntectic data generated and used to estimate the parameters  $\beta_1, \beta_2$  and  $\mu_2$ . Fig. 2a is generated by taking the model and human data, patient 9 as given in table 2 of [33]. Fig. 2b shows the best fit estimate for the model parameters  $\beta_1, \beta_2$  and  $\mu_2$ .

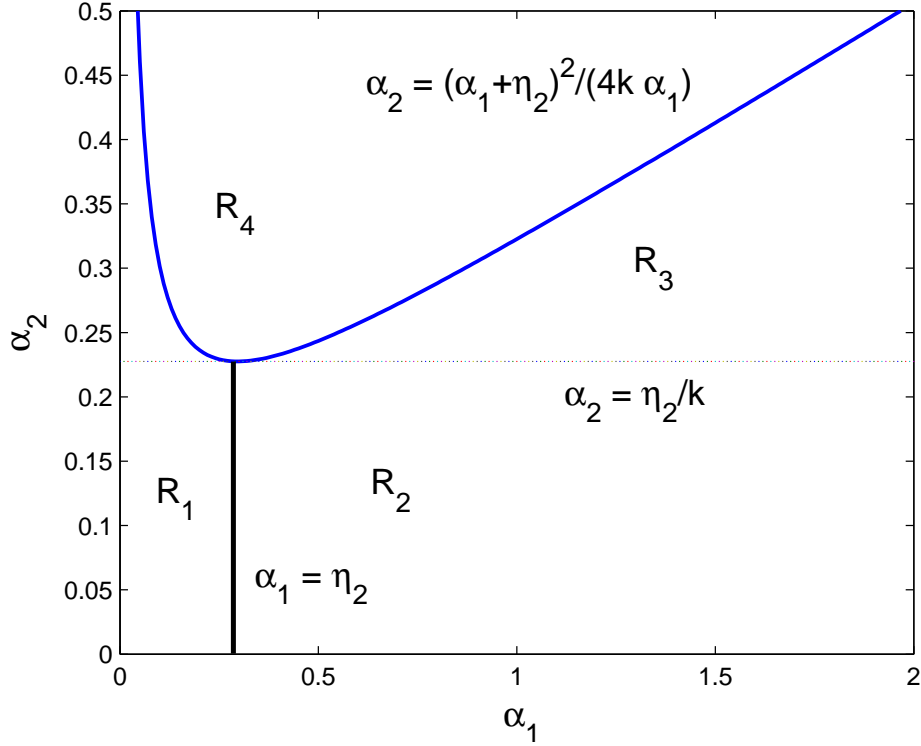


Fig. 3. The figure shows the existence and stability regions of the equilibrium points  $E_2$ ,  $E_+^*$  and  $E_-^*$ , where  $k = k_1\bar{x} + k_2\bar{y}$ .  $R_1$  ( $\alpha_1 - \eta_2 < 0$  and  $0 < \alpha_2 < \alpha_{21} = 0.227538$ ) is the region where  $E_2$  and  $E_-^*$  exist such that  $E_2$  is unstable and  $E_-^*$  is stable.  $R_2$  ( $\alpha_1 - \eta_2 > 0$  and  $0 < \alpha_2 < \alpha_{21} = 0.227538$ ), is the region where both  $E_2$  and  $E_-^*$  exist and stable (bistability region).  $R_3$  ( $\alpha_1 - \eta_2 > 0$  and  $\alpha_{21} = 0.227538 < \alpha_2 < \alpha_{22} = 1111.032892$ ) is the region where the equilibrium points  $E_2$ ,  $E_-^*$  and  $E_+^*$  exist and both  $E_2$  and  $E_-^*$  are stable (bistability region) and  $E_+^*$  is unstable. In the region  $R_4$  ( $\alpha_2 > \alpha_{22}$ ) the equilibrium point  $E_2$  exists and it is stable.

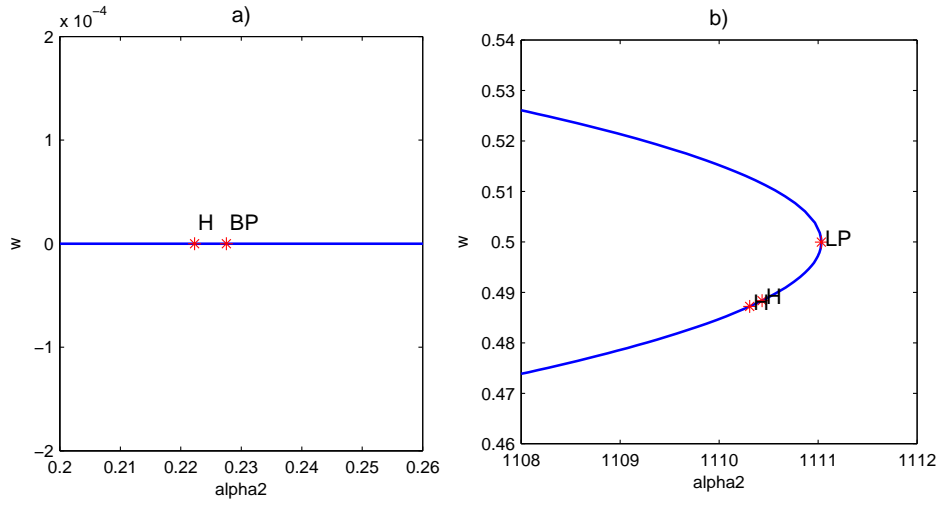


Fig. 4. The figure shows the points of bifurcation for the system parameter  $\alpha_2$ , which has been obtained using the software Matcont. Here, H represents neutral saddle, BP is the branching point and LP is the limiting point. The branching point occurs at  $\alpha_2 = 0.227538$ , which is identified as the transcritical bifurcation point and the limit point occurs at  $\alpha_2 = 1111.032892$  which is identified as the saddle node bifurcation of the system. Other system parameter values are fixed, which is given in Table 1.

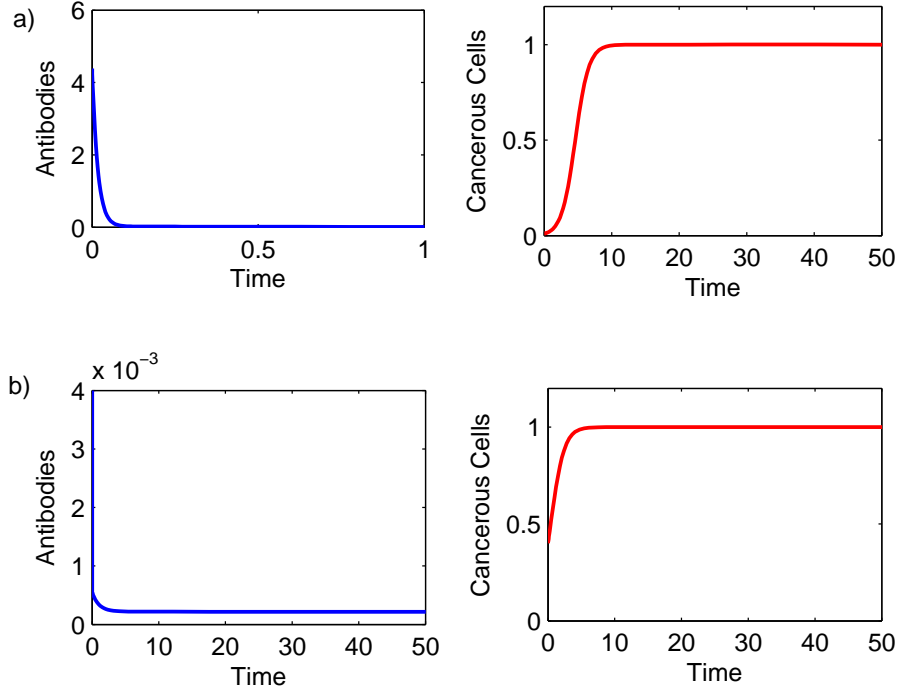


Fig. 5. The figure shows that in the region  $0 < \alpha_2 < \alpha_{21} = 0.227538$ , the unique positive interior equilibrium point  $E_-^*$  characterized by high number of cancerous cells (nearly equal to the carrying capacity  $K_2$ ) is stable. Setting  $\alpha_2 = 0.04$  with any initial conditions (a)  $IC = (0.5, 0.49, 4.39, 0.01)$  and (b)  $IC = (0.5, 0.49, 0.004, 0.5)$ , the cancerous cells grow to the high number of cancerous cells equilibrium point  $E_-^*$ .

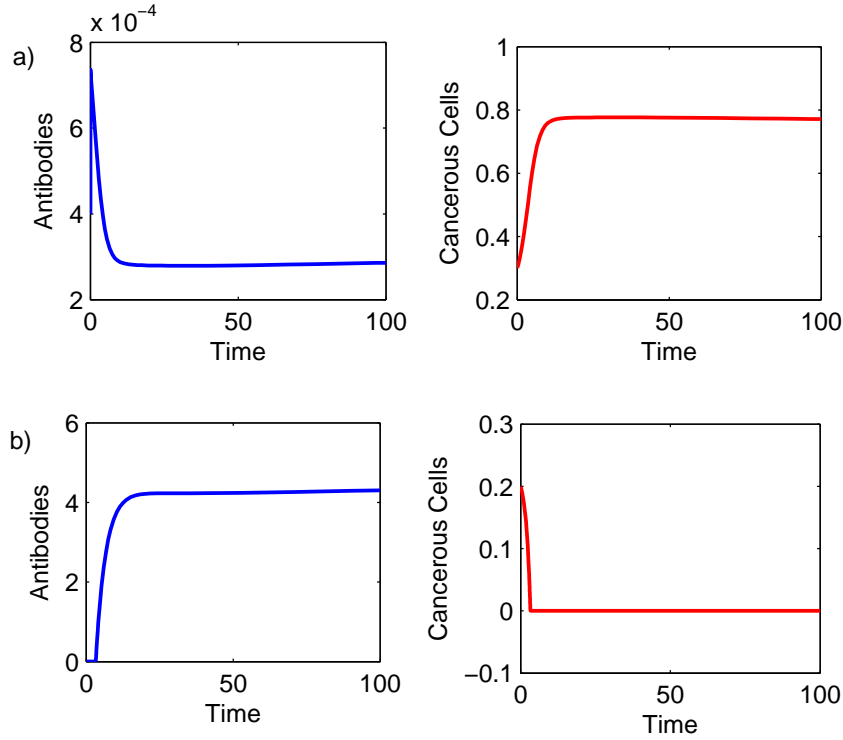


Fig. 6. The figure shows how the system is sensitive to the initial conditions in the region of bistability, that is,  $\alpha_{21} < \alpha_2 < \alpha_{22}$ . Setting  $\alpha_2 = 800$ , (a) initial conditions  $IC = (0.5, 0.49, 0.0004, 0.3)$  shows that the cancerous cells grow to the high number of cancerous cells equilibrium point  $E_-^*$ . (b) However, a fraction of cell difference in the number of cancerous cells  $IC = (0.5, 0.49, 0.0004, 0.2)$  shows that it decays to zero, to the cancerous free equilibrium point  $E_2$ .

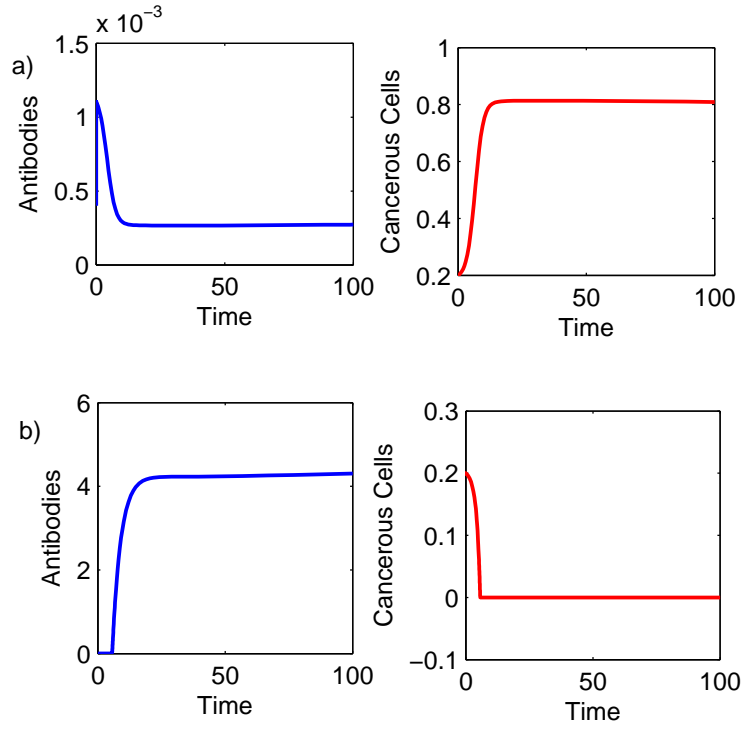


Fig. 7. The figure illustrates that with the same initial condition  $IC = (0.5, 0.49, 0.0004, 0.2)$  and for different values of  $\alpha_2$ , the system has different behavior. (a) For  $\alpha_2 = 726$ , the cancerous cells grow to the high number of cancerous cells equilibrium point and (b) for  $\alpha_2 = 727$ , it decay to the cancerous cells free equilibrium point.

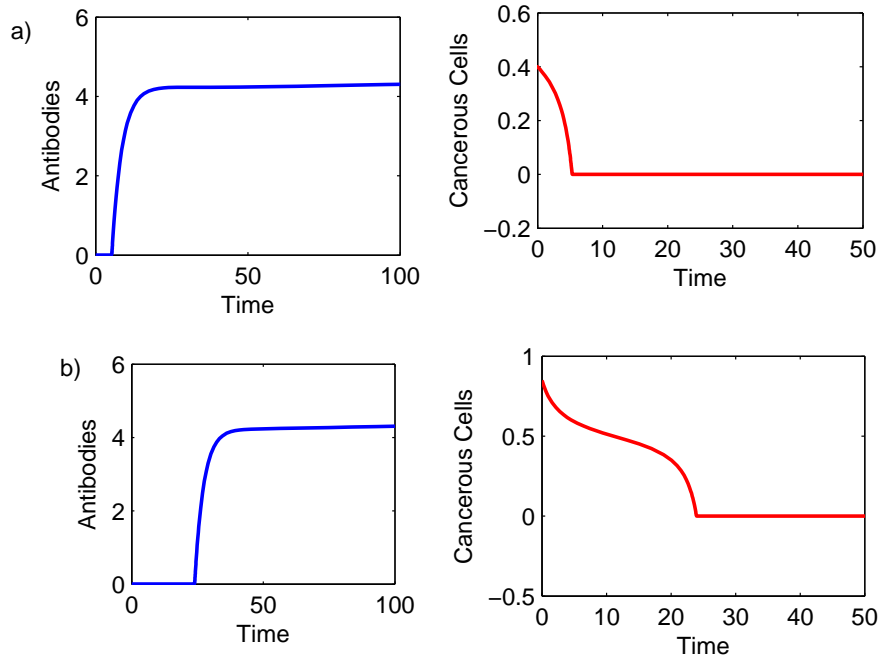


Fig. 8. The figure shows when the value of  $\alpha_2 = 1200$  greater than the critical value  $\alpha_{22} = 1111.03$  for different values of the initial conditions (a)  $IC = (0.5, 0.49, 0.0004, 0.4)$  and (b)  $IC = (0.5, 0.49, 0.0004, 0.85)$ , the cancerous cells always decay to zero.